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Tuberculosis disease in children and adolescents on therapy with anti-tumor necrosis factor-alpha agents: a collaborative, multi-centre ptbnet study

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Summary of the article's main point:

Children and adolescents on tumor necrosis factor-alpha inhibitors are prone to severe tuberculosis disease, especially miliary tuberculosis, resulting in significant morbidity. False-negative immunodiagnostic tests are common and a low threshold to initiate targeted investigations is recommended.

ABSTRACT

Background

In adults, anti-tumor-necrosis-factor (TNF)- α therapy is associated with progression of latent tuberculosis infection (LTBI) to tuberculosis (TB) disease. The existing paediatric data are very limited.

Methods

Retrospective multi-centre study within the Paediatric Tuberculosis Network European Trials Group, capturing patients <18 years who developed TB disease during anti-TNF- α therapy.

Results

Sixty-six tertiary healthcare institutions providing care for children with TB participated. Nineteen cases were identified; Crohn's disease (n=8;42%) and juvenile idiopathic arthritis (n=6;32%) were the commonest underlying conditions. Immune-based TB screening (tuberculin skin test and/or interferon-gamma release assay) was performed in 15 patients before commencing anti-TNF- α therapy, but only identified one LTBI case; 13 patients were already receiving immunosuppressants at the time of screening. The median interval between starting anti-TNF- α therapy and TB diagnosis was 13.1 (IQR:7.1-20.3) months. All cases presented with severe disease, predominately miliary TB (n=14;78%). One case was diagnosed post-mortem. TB was microbiologically confirmed in 15 cases (79%). The median duration of anti-TB treatment was 50 (IQR:46-66) weeks. Five of 15 (33%) cases who had completed TB treatment had long-term sequelae.

Conclusions

The data indicate that LTBI screening is frequently false-negative in this patient population, likely due to immunosuppressants impairing test performance. Therefore, patients with immune-mediated diseases should be screened for LTBI at the point of diagnosis, before commencing immunosuppressive medication. Children on anti-TNF- α therapy are prone to severe TB disease, and significant long-term morbidity. Those observations underscore the need for robust LTBI screening programs in this high-risk patient population, even in low TB prevalence settings.

Introduction

Etanercept was the first tumor necrosis factor-alpha (TNF)- α inhibitor to be approved for the treatment of juvenile idiopathic arthritis (JIA) in 1998, and the same year infliximab was approved for the treatment of Crohn's disease. Several other anti-TNF- α agents have been approved since, which are increasingly being used to treat children affected by JIA, inflammatory bowel disease (IBD) and other immune-mediated conditions. In these patients, both the disease itself and the use of conventional immunosuppressant drugs and/or biologic agents are associated with an increased risk of serious infections, including tuberculosis (TB) [1-3].

In the human host immune response to mycobacterial infections TNF- α plays a critical role, particularly in the formation and maintenance of TB granulomas [4]. In adults, exposure to anti-TNF- α agents has been associated with reactivation TB and progression from latent TB infection (LTBI) to TB disease, commonly manifesting as extrapulmonary or disseminated forms of TB [5]. Most current guidelines therefore emphasise the need to rule out LTBI before commencing anti-TNF- α therapy [6-8]. There is general consensus that patients who are diagnosed with LTBI based on a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result should receive anti-TB preventive therapy prior to commencing anti-TNF- α therapy. However, it currently remains uncertain if anti-TNF- α treatment has to be delayed until after the completion of preventive therapy, or whether it is safe to commence anti-TNF- α agents one or two months into preventive therapy.

Currently the data on TB disease in children receiving anti-TNF- α therapy are very limited [9]. To our knowledge, fewer than 20 cases have been described in detail in the peer-reviewed literature so far [10-16]. Concerningly, several of those cases had a fatal outcome.

Using a well-established network of paediatric specialists providing healthcare for children with TB, the aim of this study was to identify children and adolescents who developed TB disease

while receiving anti-TNF- α therapy and to describe their presentation, clinical course and outcome.

Methods

Participating centres

We conducted a retrospective multi-centre study within the Paediatric Tuberculosis Network European Trials Group (ptbnet) [17-20], a network of clinicians and researchers with an interest in paediatric TB, from September 2016 until March 2019. In March 2019 ptbnet comprised 252 members based in 32 European countries and seven countries outside Europe, making it the largest paediatric TB network globally.

Eligibility criteria and definitions

All patients aged 0 to 18 years with confirmed TB disease (*i.e.* microbiologically proven by culture or nucleic acid amplification tests) and unconfirmed TB disease, based on the consensus case definitions proposed by Graham *et al.* [21], after initiation of anti-TNF- α therapy were eligible for inclusion. Severe TB disease was defined as per previously published criteria [22]. Significant hepatotoxicity was defined as serum aspartate aminotransferase or alanine aminotransferase concentrations >5 times the upper limit of normal (ULN) in asymptomatic patients, or >3 times the ULN in patients with symptoms (abdominal pain, nausea, vomiting or jaundice)[23].

Data collection and analyses

A standardised data collection tool (**Online Supplementary Material [OSM] 1**) was designed and all ptbnet members were invited by email to contribute cases to this study in September 2016. The data collection forms received were collated into an Excel database (Microsoft, Redmond, WA, USA) hosted on a secure server. In addition, in March 2019, all ptbnet members were asked via the ptbnet online discussion forum and via email reminders to confirm that no cases fulfilling the eligibility criteria had received care at their healthcare-

institution. Categorical-variables-were-described-as-percentages, and-continuous-variables-as-medians-with-interquartile-ranges-(IQR). Confidence-intervals-(CIs)-around-proportions-were-calculated-with-the-modified-Wald-method.

Ethics approval

Ethical approval for this study was obtained from the Hospital Sant Joan de Déu (Barcelona, Spain) Ethics Committee (reference PIC 133-13). No personal or identifiable data were collected during the conduct of this study.

Results

Collaborators from 66 tertiary and quaternary healthcare institutions providing care for children with TB participated in the study. Forty-nine (74%) centres reported that they had not encountered any patients fulfilling the case definitions during the preceding 5 years (**OSM 2**). A total of 19 patients (8 male;11 female) receiving anti-TNF- α therapy diagnosed with TB disease between February 2011 and March 2019 were identified. The largest numbers of cases were reported from Spain, Germany and the United Kingdom (each n=4). One case each was reported from healthcare centres in Austria, Croatia, Latvia, Lithuania, Portugal, Switzerland and Ukraine. Two of the cases (case 3 and case 4; **Table 1**) had previously been detailed elsewhere in case reports [10,11].

Characteristics of the cases identified

The majority of the cases were Caucasian (n=15;79%) and born in the country where they were diagnosed (n=17;89%). Eleven (58%) cases had been BCG-vaccinated in the past; 8 (42%) were BCG-unvaccinated. The median age at diagnosis of the underlying inflammatory condition was 9.7 (IQR: 6.6-12.8) years. The most common underlying conditions that prompted use of anti-TNF- α therapy comprised Crohn's disease (n=8;42%) and JIA (n=6;32%), as summarised in **Table 1**.

Risk factors for TB and screening for latent TB infection

Almost half of the patients (n=9;47%) had risk factors for TB, including birth in, residence in or travel to a high TB prevalence country, residence in an urban area with high TB incidence and/or contact with an individual with TB disease before anti-TNF- α therapy was commenced. Screening for LTBI before starting anti-TNF- α therapy, either by TST or IGRA, was performed in 15 patients. Only one case had a positive TST result (case 4), and two had an indeterminate QFT-GIT result (cases 6 and 13). Two of these cases received a 9-month course of isoniazid prior to starting anti-TNF- α therapy (cases 4 and 13). Importantly, 13 (87%) of those 15 patients were receiving immunosuppressive therapy at the time when the TST and/or IGRA was performed. A chest x-ray was performed in 15 patients prior to commencing anti-TNF- α therapy; only one patient had abnormal radiological findings (case 11), comprising a calcified left supraclavicular lymph node without pulmonary changes.

Clinical presentation of TB disease

The median (IQR) age at diagnosis of TB disease was 14.3 (11.3-15.8) years. Eleven patients were receiving adalimumab, four infliximab and four etanercept at the time they were diagnosed with TB disease. The median (IQR) time interval between starting anti-TNF- α therapy and TB being diagnosed was 13.1 (7.1-20.3) months. Six (32%) patients (including four who had previously been screened for LTBI) had new risk factors for TB that occurred after commencing anti-TNF- α therapy, comprising recent contact with a TB disease case (n=4) and travel to a high TB prevalence country (n=2); in the remaining 13 (68%) patients no new risk factors were identified. In 6 (32%) of the patients, no risk factors for TB were identified either at initiation of anti-TNF- α therapy or subsequently.

All patients presented with predefined severe disease, including miliary TB (n=14;74%), abdominal TB (n=8;42%), central nervous system TB (n=4;21%), pulmonary cavitation (n=4;21%), pericarditis (n=4;21%), osteoarticular TB (n=2;11%) and eye disease (n=1;5%).

Additional, non-severe disease manifestations comprised peripheral lymphadenitis (n=4;21%) and pleuritis (n=3;16%).

The median (IQR) time interval between onset of symptoms and TB diagnosis was 3.3 (2.0-7.3) weeks. One patient was only diagnosed at a post-mortem examination (case 10). In 15 (79%) of the cases TB disease was microbiologically-confirmed by culture or nucleic acid amplification tests; the remaining 4 (21%) cases were diagnosed with TB disease based on symptoms and radiological findings consistent with TB.

Of the non-confirmed cases, case 8 presented with fever and weight loss, and imaging revealed wide-spread miliary lesions in the lungs, liver and spleen; the initial IGRA result was indeterminate, but on re-testing the IGRA result converted to positive. Case 12 had intermittent fevers and weight loss, abnormal abdominal MRI findings and showed IGRA result conversion. Case 16 presented with fever and respiratory distress, and imaging revealed bilateral basal consolidation and right-sided pleural effusion; both TST and IGRA results were negative. Case 19 presented with fever, cough, weight loss and diarrhoea, chest x-rays showed miliary changes and the IGRA result converted. All 4 patients responded to anti-TB treatment, with complete resolution of their constitutional symptoms.

Performance of immune-based TB tests at presentation

In 16 patients one or more immune-based TB test were performed when they presented with TB disease. A TST was performed in 6 patients; four had a positive, while two had a negative test result (case 4 already had a positive TST at baseline LTBI screening, but the induration diameter increased from 10 to 30 mm). A QFT assay was performed in 9 patients; 5 had a positive, two a negative and two an indeterminate test result. Only two patients had a T-SPOT.TB assay performed; both were positive. Therefore, the test sensitivities of TST, QFT assays and T-SPOT.TB assays at presentation with TB disease were 66.7% (95%CI: 29.6-90.1%), 55.6% (95%CI: 26.6-81.1%) and 100% (95%CI: 29.0-100%), respectively.

Treatment of TB disease

One case was diagnosed post-mortem and never received anti-TB treatment (case 10). All remaining 18 patients were initially commenced on quadruple anti-TB treatment with rifampicin, isoniazid, pyrazinamide and ethambutol; one case was switched to another regimen after 3 days (case 17). The median (IQR) duration of anti-TB treatment was 50 (46-66) weeks. Although all isolated *M. tuberculosis* strains were susceptible to first-line oral anti-TB agents, second line drugs were used in 7 cases, either before the sensitivity pattern was known (due to concerns regarding possible drug-resistance), or because of toxicity with first line agents. Four patients experienced drug-induced adverse events related to anti-TB treatment, including significant hepatotoxicity (cases 4, 6 and 11), leukopenia (case 9), persistent blurred vision attributed to ethambutol (case 11), and hearing impairment that resolved after discontinuation of amikacin (case 6). Only one patient (case 4) underwent surgical intervention.

Additional treatment

Anti-TNF- α therapy was discontinued at TB diagnosis in all patients, except for one (case 15). Thirteen patients were commenced on corticosteroids, either as adjunctive treatment for TB disease and/or to treat flare-ups of their underlying immune-mediated disease. Five patients were commenced on other anti-inflammatory drugs to manage their underlying disease.

Outcome

Of the 18 patients who were alive at presentation, 10 (56%) were cured without long-term sequelae, 2 (11%) are still on anti-TB treatment with good clinical progress and 5 (28%) were cured but have significant long-term sequelae resulting from TB disease, including pulmonary fibrosis/cavitation (cases 2 and 7), persistent visual problems (case 11), restricted movement in the knee joint (case 4) and spinal instability (case 16). One case was lost to follow-up while still receiving treatment (case 18). Only in 4 patients anti-TNF- α treatment was subsequently

reintroduced after completion of TB treatment (cases 7, 12, 14 and 17), without any adverse events.

Discussion

To our knowledge, this is the largest study of TB disease associated with anti-TNF- α therapy in paediatric patients to date. The fact that only 19 cases were reported throughout our network indicates that TB disease may be a less common complication in children on anti-TNF- α therapy than in adults, considering the large number of specialist centres involved in this study.

The relatively low number of TB cases may be the result of one or several of the following factors: a) lower incidence of LTBI in children compared with adults, b) low background TB prevalence in countries where anti-TNF- α agents are commonly used (which applies to all Northern, Western and Southern European countries), and c) successful implementation of LTBI screening prior to commencing anti-TNF- α therapy in the paediatric setting. Of the 32 European countries where ptbnet members are based currently, only five are high TB prevalence countries – Lithuania (TB notifications in 2018: 49.9/100,000), Moldova (101.8/100,000), Romania (68.5/100,000), Russia (84.1/100,000), and Ukraine (76.7/100,000); the majority of the remaining 27 countries have TB incidences below 10.0/100,000 [24]. Given that anti-TNF- α agent use in children was uncommon for the first years after etanercept and infliximab had been approved, relatively few children would have received those drugs before the first report showing a strong association between anti-TNF- α agents and TB disease was published [25]. Following that report, routine LTBI screening prior to anti-TNF- α therapy, both in adults and in children, was incorporated into most national and international guidelines [6, 26].

Recent data from other studies further support the notion that TB disease is a relatively uncommon complication of anti-TNF- α therapy in children and adolescents in Europe. A multi-centre study in Finland that included 348 patients with JIA, the majority of which were children

and adolescents at the time anti-TNF- α therapy was commenced, did not identify any cases of TB disease [27]. A German registry-based study that included 3350 paediatric patients with rheumatological conditions who received anti-TNF- α agents did also not identify any patients with TB disease [28]. Recently, a pharmacovigilance study that combined the data of 15,284 JIA patients from different registries reported 14 cases of TB disease among children and adolescents receiving anti-TNF- α agents, although no details on disease manifestations were included [29]. Additional data kindly provided by the senior author (N. Ruperto; personal communication) revealed that only 12 of those cases had occurred in Europe, and that cases reported from the Russian Federation, where ptbnet currently only has one participating centre, accounted for the majority of those cases (n=7), providing further reassurance regarding the robustness of our data.

Our study highlights the great severity of TB disease in children on anti-TNF- α therapy, consistent with previous case reports [10, 13-16]. All patients captured by our study presented with severe disease. Three quarters had miliary TB, which is associated with significant morbidity and mortality. This finding stands in stark contrast to TB disease in immunocompetent individuals, where miliary TB accounts for only about 2% of cases overall [30].

Our study demonstrates the importance of routine LTBI screening in paediatric patients prior to commencing anti-TNF- α therapy, and simultaneously highlights the limitations of immune-based LTBI screening in patients who are already receiving immunosuppressive therapy. Of the 15 cases screened for LTBI among our cohort, only one had a positive test result. Of the remaining 14 patients, only 4 reported additional risk factors for acquiring TB after screening, comprising contact with an individual with TB disease and travel to a high TB prevalence country (n=3 and n=1, respectively). In those 4 patients *de novo* infection acquired after the screening procedure appears likely. Considering the absence of new risk factors after LTBI screening in the remaining 10 cases, reactivation of latent infection is the most likely underlying

mechanism. As most of those patients were receiving immunosuppressive treatment (other than anti-TNF- α agents) prior to LTBI screening, it is likely that their screening test results were false-negative, as both TSTs and IGRAs rely on the detection of intact anti-mycobacterial immune responses.

Our data also highlight the suboptimal performance of TSTs and IGRAs as adjunctive tests in the diagnostic workup for suspected TB disease in patients on anti-TNF- α therapy. Although the number of test results available was relatively small, resulting in estimates with wide confidence intervals, the data indicate that only approximately half of those patients have a positive QFT assay result, a far lower proportion than previously reported in immunocompetent children [31]. This observation is in concordance with a recent study that showed that anti-TNF- α agents impair the performance of QFT assays substantially [32].

It is well documented that the performance of TSTs is impaired in immunocompromised individuals, including patients with primary or secondary immunodeficiency and patients on immunosuppressive therapy [33]. Although some authors have stipulated that the performance of IGRAs is maintained in immunosuppressed individuals, recent data from *in vitro* studies show that a range of immunosuppressive agents - including corticosteroids, infliximab and calcineurin inhibitors - have a detrimental impact on IGRA performance, resulting in false-negative test results in a substantial proportion of patients [32, 34, 35]. Therefore, as highlighted previously [36], we strongly believe that patients with immune-mediated inflammatory conditions should be screened for LTBI at the point when their diagnosis is established before commencing any immunosuppressive medication, as also suggested by a recent guideline [37]. Following initiation of immunosuppressive therapy, patients should be tested simultaneously with a TST and an IGRA to achieve greater sensitivity [36]. In this setting positive TST or IGRA test results remain useful for management decisions, but negative test results become uninterpretable, as it is currently impossible to determine whether a negative result in this

setting reflects absence of TB infection or alternatively a false-negative result caused by the inhibitory action of the immunosuppressive medication.

Current guidelines do not recommend repeat LTBI screening at regular intervals, unless the patient develops symptoms consistent with TB or has new risk factors [7, 37]. Notably, nearly one third of the cases in our cohort had new risk factors after starting anti-TNF- α therapy, comprising known TB contact or overseas travel. Therefore, we believe that it is important to enquire about new TB risk factors at each patient contact during anti-TNF- α therapy. In patients who report a new risk factor, LTBI screening should be performed with a TST and an IGRA. If either test result is positive, LTBI treatment should be commenced once TB disease has been ruled out. In patients with concordantly negative results, clinicians should decide whether or not to start LTBI treatment based on a risk assessment (i.e. age of the patient, infectiousness of the index case, intensity of contact).

Only four of the patients were recommenced on anti-TNF- α treatment after completion of active TB treatment; two continued on isoniazid as prophylaxis, while the remaining did not continue on any anti-TB drugs. None of these patients developed recurrence of TB. Given the limited published experience on re-introduction of anti-TNF- α agents after TB disease, it currently remains uncertain whether or not 'secondary' prophylaxis is warranted routinely.

The main limitation of this study is its retrospective design, which can result in recall bias. However, it appears unlikely that any of the participating TB experts would not have recalled a patient who developed TB disease while receiving anti-TNF- α agents, as this is a well-known risk factor. Furthermore, our methodology does not allow us to estimate the incidence of TB disease in children receiving anti-TNF- α therapy as the denominator (i.e. number of children receiving anti-TNF- α therapy across all centres) is unknown. Additionally, we cannot exclude that further cases presented to other healthcare institutions that did not participate in this study. However, for many countries one or several leading national paediatric TB centres participated

in this study, and it appears unlikely that those centres would not have been contacted for advice if a case had occurred elsewhere in the country. Finally, we can not exclude that there were additional cases with subclinical TB disease that were not diagnosed or cases who died before a diagnosis was established.

In summary, our data indicate that TB disease may be less common in children and adolescents receiving anti-TNF- α therapy than in adults. However, the data show that children on anti-TNF- α therapy who develop active TB are prone to severe TB disease, especially miliary TB. The disease severity and the short- and long-term morbidity observed in those patients underscores the need for robust LTBI screening programs in this high-risk patient population, even in low TB prevalence settings. Both patients receiving anti-TNF- α drugs and prescribing physicians need to be aware of the risks related to TB, and have a low threshold to initiate targeted investigations should a patient have new risk factors or develop symptoms compatible with TB disease. Additional, prospective research is needed to determine whether regular LTBI screening during anti-TNF- α therapy can help to further reduce the incidence of TB disease in children on long-term treatment.

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Conflicts of interest

MT has received QuantiFERON assays at reduced pricing or free of charge for TB diagnostics projects from the manufacturer (Cellestis/Qiagen), and has received support for conference attendance from Cepheid. The manufacturers had no influence on the study design, data interpretation, writing of the manuscript or decision to submit the data for publication. The rest of authors do not have conflicts of interest to disclose.

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Table 1. Details of patients with TB disease following initiation of anti-TNF α therapy

| | Gender, ethnicity, BCG vaccination history | Underlying disease, age at diagnosis (years) | Risk factors and medication at LTBI screening prior to anti-TNF α therapy | Anti-TNF- α drug used, age at initiation (years) | Age at TB diagnosis (years), new risk factors | Details regarding TB disease and diagnostic tests at presentation | Anti-TB and anti-inflammatory drugs used, duration of treatment (weeks) | TB outcome |
|---|--|--|---|---|---|--|---|--------------------------------------|
| 1 | F, Caucasian, yes | JIA, 1.3 | No risk factors; TST 3mm, negative QFT-GIT, normal CXR; on MTX | ADA (5.2) | 5.8, TB contact | Miliary TB diagnosed after 9 days of fever, cough and anorexia. Positive QFT-GIT, sputum PCR-positive (cultures no growth) | HRZE (14); HRZ (18) Steroids (12) for arthritis and uveitis flare; also MTX and ibuprofen Recommended on R (65) as 'secondary' prophylaxis when immunosuppression was restarted | Cured without sequelae |
| 2 | F, Caucasian, yes | Systemic JIA, 3.0 | Born and living in high TB prevalence country; negative TST, normal CXR; on meloxicam and MTX | ETN (9.0) | 12.1, none | Cavitary lesion in left upper lobe after 2 weeks of fever, fatigue, cough and anorexia; also developed left pleuritis, pericarditis and nodules in right lobe 4 weeks after initiation of anti-TB agents (probable immune reconstitution syndrome). TST 15mm, sputum culture- and PCR-positive (fully-susceptible MTB) | HRZE+OFLO+AMIK (4); HRZE (8); HRE (36) Steroids (42) and MTX for JIA flare | Cured, pulmonary cavity and fibrosis |
| 3 | M, Caucasian, yes | Poly-articular JIA, 4.0 | Born and living in high TB prevalence country; negative T-SPOT.TB, normal CXR; on MTX | ADA (8.1) | 8.6, none | Miliary TB with pleural & pericardial effusion and ascites diagnosed after 4 weeks of fever, cough, headache, joint pain, abdominal distention, and weight loss. Positive T-SPOT.TB, gastric aspirates culture- and PCR-positive (fully-susceptible MTB) | HRZE (10); HRE (37) Steroids (10) for arthritis and polyserositis; also MTX and NSAIDs | Cured without sequelae |

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| 4 | F, Caucasian, no | Oligo-articular JIA, 5.7 | TB contact; positive TST (10mm), normal CXR; on MTX and steroids. Received H for 9 months. | ETN (7.0); ADA (9.3) | 9.6, TB contact | Miliary TB diagnosed after 2 weeks of fever, left inguinal lymphadenitis and arthritis in left knee; TST 30mm, synovial biopsy PCR-positive, gastric aspirates culture-positive (fully-susceptible MTB) | HRZE (8); HR (18); treatment interruption due to significant hepatitis (4); HR (47) Also had knee synovectomy and inguinal lymph node excision, Steroids (8) for tuberculomas and arthritis | Cured, restricted range of movement in knee joint |
| 5 | F, Caucasian, no | JIA, 7.2 | No risk factors; negative QFT-GIT, normal CXR, on MTX and steroids | ETN (8.3) | 9.3, TB contact | Miliary TB, abdominal disease, cervical adenitis and erythema nodosum after 4 weeks of cough, anorexia and abdominal pain. Positive QFT-GIT, lymph node tissues culture- and PCR-positive (fully-susceptible MTB) | HRZE (8); HR (41) Steroids (6) for miliary TB | Cured without sequelae |
| 6 | F, Caucasian, yes | JIA, 9.8 | Born in high TB prevalence country; indeterminate QFT-GIT, normal CXR, on steroids | ETN (14.3) | 15.1, none | Miliary TB, inguinal lymphadenitis, abdominal disease, brain tuberculoma and spinal TB after 8 weeks of fever, weight loss and malaise. Indeterminate QFT-GIT, sputum culture- and PCR-positive (fully- susceptible MTB) | HRZE+AMIK+MOXI (9); HR+MOXI (41); Z stopped due to significant hepatitis; AMIK stopped due to hearing impairment Adherence issues Steroids for miliary TB | Cured, spinal instability |
| 7 | M, Caucasian, no | Crohn's disease, 8.8 | No risk factors; negative QFT-GIT, on steroids | IFX (13.9) | 14.7, none | Cavitating lesion, airway compression and cervical lymphadenitis after 11 weeks of cough, anorexia and night sweats. Negative QFT-GIT, sputum culture- and PCR-positive (fully- susceptible MTB) | HRZE (12); HR (24) Steroids to treat airway compression and Crohn's disease IFX reinitiated 7 months after TB treatment completion | Cured, pulmonary fibrosis |

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| 8 | F, Asian, yes | Crohn's disease, 9.7 | Family from and travel to high TB prevalence country; negative QFT-GIT, on AZA and mesalazine | ADA (12.4) | 13.7, trip to high TB prevalence country | Miliary TB diagnosed after 3 weeks of fever, cough and weight loss. Chest x-ray and abdominal ultrasound showed miliary lesions. Indeterminate QFT-GIT initially (repeat after 8 weeks of anti-TB treatment positive), cultures no growth | HRZE (12); HR (40) No steroids | Cured without sequelae |
| 9 | M, Caucasian, no | Crohn's disease, 11.6 | No risk factors; no TST/IGRA done, normal CXR; on MTX and steroids | IFX (14.0); ADA (14.9) | 15.8, trip to high TB prevalence country | Miliary TB diagnosed after 4 weeks of fever, cough and weight loss. TST 10mm, sputum PCR-positive | HRZE (13); HR, then H+RIFAB, then H+LEVO due to leukopenia (142 in total) No steroids | Cured without sequelae; PCR-confirmed cutaneous TB at age 20.3 years (probable recurrence; no new risk factors) |
| 10 | F, Caucasian, no | Crohn's disease, 11.6 | Lived in an urban area with a TB incidence of 70.0/100,000; negative TST, normal CXR; no immunosuppressive medication | ADA (12.2) | 12.3, none | 4 weeks of fever and per-rectal bleeding; managed as flare of Crohn's disease with immunosuppression and surgery, without improvement. Pulmonary haemorrhage and multiorgan failure; died after 3 weeks. Miliary TB was diagnosed post-mortem; liver, spleen and gut tissue PCR-positive | TB treatment never initiated | Died |
| 11 | F, Asian, yes | Crohn's disease, 13.0 | Family from and travel to high TB prevalence country, known TB contact; no TST/IGRA done, abnormal CXR; on steroids and AZA | IFX (14.2) | 14.3, none | Cavitary pulmonary TB diagnosed after 1 week of fever, headaches, cough and night sweats. Positive T-SPOT.TB, sputum culture- and PCR-positive (fully-susceptible MTB) | HRZE (2), then HE+MOXI+AMIKA due to significant hepatitis (2); HE+MOXI (61); H+MOXI due to blurred vision (17) No steroids | Cured, pulmonary cavity and persistent blurred vision |

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| 12 | M, Asian, yes | Crohn's disease, 13.6 | No risk factors; negative QFT-GIT, normal CXR; on steroids and AZA | IFX (17.1) | 17.1, none | Abdominal TB diagnosed after 6 months of intermittent fever, abdominal pain, weight loss, vomiting and diarrhea. Positive QFT-GIT, cultures no growth | HRZE (9); HR (20) No steroids Continued on H when IFX was reinitiated after TB treatment completion | Cured without sequelae |
| 13 | M, Caucasian, yes | Crohn's disease, 13.7 | No risk factors; indeterminate QFT-GIT, normal CXR; no immunosuppressive medication. Received H for 9 months. | IFX (15.8) | 17.6, none | Miliary TB with upper left lobe consolidation and splenic nodules after 2 weeks of fever, cough and pleuritic chest pain. Sputum culture- and PCR-positive (fully-susceptible MTB) | HRZE+AMIK+LEVO (17); HR (35) Steroids (38) for persistent fever and Crohn's flare | Good clinical progress (still on TB treatment) |
| 14 | M, Caucasian & Caribbean, yes | Crohn's disease & primary sclerosing cholangitis, 13.3 | No risk factors; negative T-SPOT. TB, normal CXR, on AZA | IFX (14.9); ADA (15.3) | 16.1, none | Lower left lobe and lingula consolidation with multiple parenchymal abscesses, pericarditis and splenic nodules after 16 weeks of gradually progressive dyspnoea, chest pain, cough, fever, weight loss and night sweats. Positive T-SPOT. TB, lung biopsy tissue PCR-positive | HRZE+CLARITHRO+AMIK (3); HRE (18); HR (38) No steroids Continued on H when IFX was reinitiated after TB treatment completion | Cured without sequelae |
| 15 | F, Caucasian, yes | Ulcerative colitis, 8.0 | Born and living in high TB prevalence country; no LTBI screening done (years earlier normal CXR and TST 10mm). Did not receive anti-TB treatment | Alternating IFX and ADA (9.3) | 10.6, none | Miliary TB, pleural and pericardial effusions after 3 weeks of fever, weight loss, worsening intestinal symptoms and cough. Streptomycin-resistant MTB in gastric aspirates | HRZE+QUINOLONONES (23); RZ (9); HR (14) Steroids and mesalazine for colitis flare ADA was not interrupted | Cured without sequelae |

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| 16 | F, Latin American, yes | UCTD, 14.2 | Born in high TB prevalence country; negative QFT-GIT, normal CXR; on MTX | ETN (15.6) | 15.9, none | Pleural TB diagnosed after one week of fever and respiratory distress (bilateral basal infiltrates). TST and QFT-GIT negative; sputum culture- and PCR-negative | HRZE (8); HR (20) Steroids (6) for pleuritis; also tacrolimus and MMF | Cured without sequelae |
| 17 | M, Caucasian, no | Psoriasis vulgaris guttata, 12.6 | No risk factors; no TST/IGRA done, normal CXR; no immunosuppressive medication | ADA (13.7) | 14.7, none | Miliary TB with abdominal and CNS involvement diagnosed after 8 weeks of fever, cough, headaches, dizziness and weight loss. TST 12mm, positive QFT-GIT, sputum PCR- and culture-positive (fully-susceptible MTB) | HRZE (3 days); HRZ+MOXI (16); HR (41) Steroids (8) for tuberculomas ADA reinitiated 12 months after TB treatment completion | Cured without sequelae |
| 18 | M, Caucasian, no | Dermatomyositis, 6.0 | No risk factors; negative TST, normal CXR; on tacrolimus and steroids | ETN (11.0); ADA (12.5) | 17.1, TB contact | Miliary TB diagnosed after 10 weeks of fever, cough and headaches. Negative TST, sputum culture-positive (fully-susceptible MTB), CSF culture- and PCR-negative | HRZE (9); HR (poor adherence, intermittently 126) Steroids (8) for meningeal and choroidal disease | Lost to follow-up 31 months after diagnosis |
| 19 | F, Caucasian, no | Chronic anterior uveitis, 7.7 | No risk factors; negative QFT-GIT; on MTX | ADA (11.5) | 11.9, none | Miliary TB after 5 weeks of fever, weight loss, cough and diarrhea. Positive QFT-GIT; gastric aspirates culture- and PCR-negative | HRZE (4); HR (43) Steroids (33) | Good clinical progress (still on TB treatment) |

ADA, adalimumab; AMIK, amikacin; AZA, azathioprine; CLARITHRO, clarithromycin; CNS, central nervous system; CXR, chest x-ray; ETN, etanercept; E, ethambutol; F, female; H, isoniazid; IGRA, interferon-gamma release assay; IFX, infliximab; JIA, juvenile idiopathic arthritis; LTBI, latent tuberculosis infection; LEVO, levofloxacin; M, male; MOXI, moxifloxacin; MMF, mycophenolate mofetil; MTB, *Mycobacterium tuberculosis*; MTX, methotrexate; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; OFLO, ofloxacin; PCR, polymerase chain reaction; QFT-GIT, QuantiFERON Gold-in-Tube (Cellestis/Qiagen; Carnegie, Australia); RIFAB, rifabutin; R, rifampicin; TB, tuberculosis; T-SPOT.TB (Oxford, Immunotec Ltd.; Oxford, UK); TST, tuberculin skin test; UCTD, undifferentiated connective tissue disease; Z, pyrazinamide

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